Efficient Syntheses of Angularly Fused Triquinanes via β-Amino-Substituted α,β-Unsaturated Fischer-Carbene Complexes

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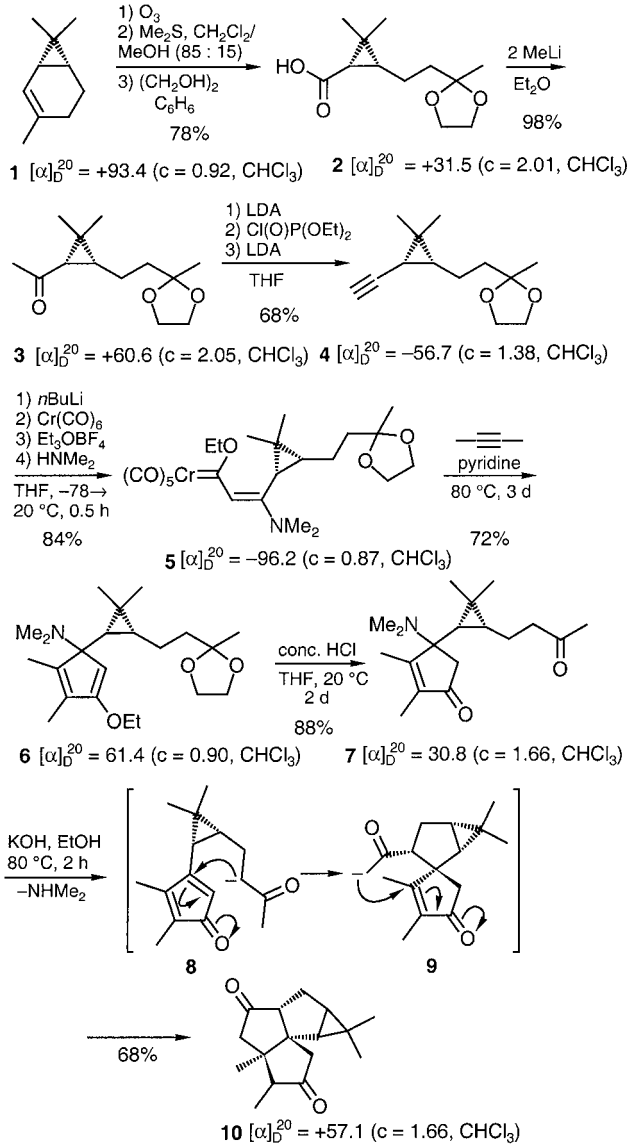
Abstract: Formal [3+2] cycloadditions of the carbene ligand in the new (3-dimethylamino-1-alkoxyalkenylidene)pentacarbonylchromium complexes **5** and **14** both with cyclopropyl substituents in the 3-position, onto alkynes give 5-dimethylamino-3-ethoxycyclopentadienes **6** and **15a–f**, the latter along with regioisomers **16a–d**, in good yields (55–72%). Treatment of these with hydrochloric acid liberates two carbonyl groups in each of them, and the resulting 5-dimethylaminocyclopent-1-en-3-ones **7** and **17a–c**/**18a–c**, under basic conditions, undergo a cascade of two cyclizations, to yield angularly fused triquinanes **10** (68%) and **23a–c** (30–97%). The overall procedure consists of four operational steps and produces cyclopropane-annelated tricyclo[6.3.0.0^{1,5}]undecane skeletons from two different alkynes each in 22–47% overall yield.

Key words: carbenechromium complexes, cycloadditions, cyclopentadienones, cascade reactions, spiro[4.4]nonenones, triquinanes

Within the last two decades, a number of new methods for the assembly of five-membered carbocycles have been developed.[1–3] Among them, the formal [3+2] cycloaddition of a (1-alkoxy-3-dialkylaminopropenylidene)pentacarbonylchromium complex to an alkyne appears to be particularly versatile, as it readily provides di- and trisubstituted 3-alkoxy-5-dialkylaminocyclopentadienes, which are protected cyclopentenones and essentially even synthetic equivalents of cyclopentadienones.[2–4] Due to a high degree of functional group compatibility of the latter method, oligofunctional cyclopentenones can easily be accessed and further elaborated to yield bicyclic skeletons.[5] In view of the considerable number of sesquiterpenes with an angularly fused triquinane skeleton,[6] we developed a new short access to such skeletons based on our [3+2] cycloaddition methodology.

A great variety of β-dialkylamino-substituted α,β-unsaturated Fischer carbene complexes is readily available by the newly developed four-step one-pot operation from terminal alkynes, $Cr(CO)_6$, Et_3OBF_4 and a secondary amine.[5] Thus, the functionally substituted enantiomerically pure 2-ethynyl-3,3-dimethylcyclopropane derivative **4**, prepared in three simple operations (for six steps) with an overall yield of 52% from commercially available (+)-2-carene **1**[7] (Scheme 1), was converted to the Fischer carbene complex **5** in 84% yield.[10]

Treatment of complex **5** with 2-butyne in pyridine at 80 °C gave the 5-(dimethylamino)-3-ethoxycyclopentadiene **6** as a 1:1 mixture of two diastereomers in 72% yield



Scheme 1

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(Scheme 1). The enol ether and the acetal moiety in **6** were hydrolyzed with concentrated hydrochloric acid in tetrahydrofuran to give the diketone **7** (88%). Subjecting **7** to basic conditions (KOH, EtOH) at elevated temperature (80 °C) set off a cascade of reactions with two consecutive cyclizations, leading to the angular triquinane **10** in 68% yield.

Mechanistically, this reaction sequence must be initiated by base-promoted elimination of dimethylamine from both diastereomers of **6** to yield a highly reactive cyclopentadienone as a common intermediate which, after deprotonation to the enolate **8**, undergoes an intramolecular Michael addition to give the spiro[4.4]nonenone skeleton of **9** (Scheme 1). The newly formed enolate **9** then cyclizes once more by an intramolecular Michael addition to form the third five-membered ring. It is obvious that the formation of the spiro[4.4]nonenone via the thermodynamically more stable enolate **8** is kinetically favored over formation of a spiro[6.4]undecenone via the regioisomeric enolate, and over the intermolecular [4+2] dimerization.[11] Both cyclization steps in this sequence proceeded with complete diastereoselectivity so that a single enantiomer with four new stereocenters resulted from the enantiomerically pure alkyne **4**. The absolute configuration of **10** was established on the basis of an X-ray crystal structure analysis and the known configuration of the starting (+)-2-carene **1** (see Figure).[12]

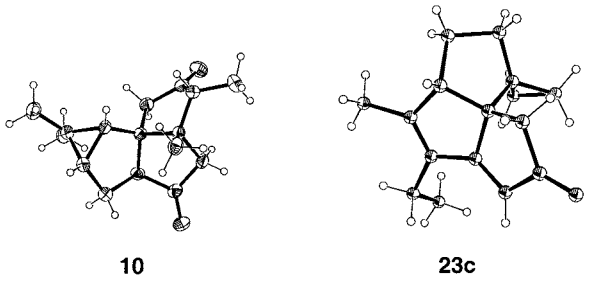
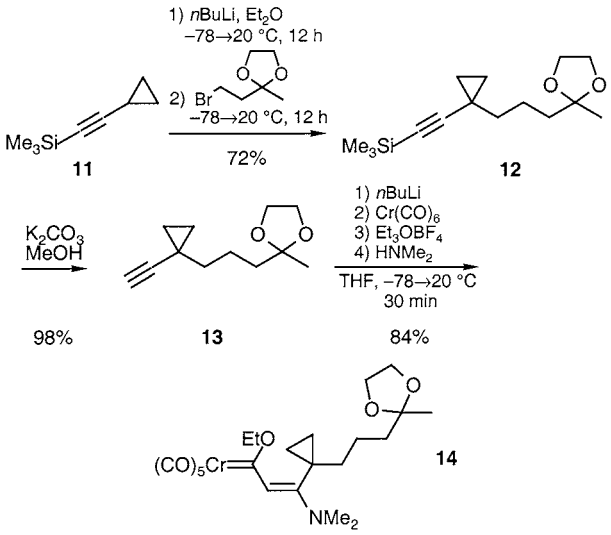


Figure Structures of angularly fused triquinanes **10** and **23c** in the crystals.[12]

Although compound **10** is formally a sesquiterpene with one additional methyl group, this tetracyclo[6.4.0.0^{1,5}.0^{10,12}]dodecane skeleton has not been found in nature. In order to access just the tricyclo[6.3.0.0^{1,5}]undecane skeleton contained in many triquinane sesquiterpenes, an alkyne starting material analogous to **4**, but without the bridging dimethylcyclopropane ring would have to be used. While this alkyne could easily be prepared in two steps from 1-trimethylsilylpropyne, it failed to yield the α,β-unsaturated β-dimethylamino-substituted carbene complex of type **5**.

Therefore, the terminal alkyne **13**, with a 1,1-disubstituted cyclopropyl group mimicking a *gem*-dimethyl substitution[13] in the propargylic position, was prepared in three steps from 2-(trimethylsilyl)cyclopropylacetylene,[14] and converted by the one-pot procedure[6] to the corresponding β-dimethylamino-substituted complex **14** (84%) (Scheme 2).

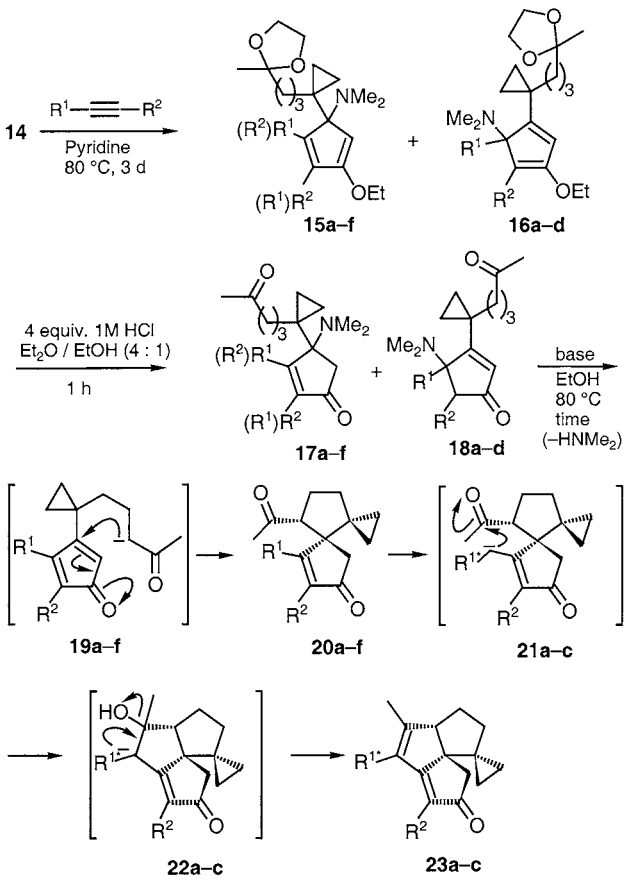


Scheme 2

Surprisingly, the cocyclizations of **14** with 2-butyne, 3-hexyne, 1-pentyne, and 3-methyl-1-butyne did not only yield the usual 1,2-dialkyl-3-ethoxy-5-dimethylaminocyclopentadienes **15a–d** but also the isomeric products **16a–d** with the dimethylamino function at the same carbon atom as one of the residues from the incoming alkyne (Scheme 3). The cocyclization with cyclopropylacetylene yielded two regioisomers of type **15** which differed only in the position of the cyclopropyl group, and diphenylacetylene gave only the single isomer **15f**.

The isomers **15a,b** and **16a,b** obtained from 2-butyne and 3-hexyne could be separated by column chromatography on silica gel. The enol ether and acetal moieties in compounds **15** and **16** were cleaved with 1 M hydrochloric acid in diethyl ether–ethanol (4:1). Under basic conditions (KOH, EtOH) at elevated temperature (80 °C) the obtained cyclopentenones **17a,b** and **18a,b** also underwent cascade bicyclizations, in each case giving the same product, **23a** and **23b**, respectively (Scheme 3). The mixture of cyclopentenones **17c**/**18c** obtained from the unseparated mixture of regiomers **15c**/**16c** could be transformed to the angular triquinane **23c** in 65% yield under the same basic conditions. The structure of **23c** was rigorously proved by an X-ray crystal structure analysis (see Figure).[12]

The angular triquinanes **23a–c** must arise from the cyclopentenones **17a–c**/**18a–c** in a mode which is different from that for the formation of **10**. The first two steps are the same, in that elimination of dimethylamine produces a cyclopentadienone **19** which cyclizes to a spiro[4.4]nonenone **20** by an intramolecular Michael addition of the enolate **19**. In fact, in the case of **17b** and **18b**, the corresponding spiro[4.4]nonenone **20b** could be isolated along with the final product **23b** after a shorter reaction time (30 min). The second cyclization, however, must occur via the vinylogous enolates **21a–c**, rather than an enolate analogous to **9**, and the cyclization step then corresponds to a vinylogous intramolecular aldol condensation. Spiro[4.4]nonenones **20d–f** were obtained as final pro-



Scheme 3 For details see table.

ducts when cyclopentadienes **15d–f**/**16d–f** arising from cocyclization of **14** with 3-methyl-1-butyne, cyclopropylacetylene and diphenylacetylene, respectively, were transformed by treatment with acid and then base.

In conclusion, an efficient new approach to oligosubstituted angular triquinane systems has been developed. This procedure may be useful for efficient syntheses of some naturally occurring sesquiterpenes[6] with such a tricyclo[6.3.0.0^{1,5}]undecane skeleton (e. g. pentalenene[15]) or analogues thereof.

References and Notes

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(6) Review: Metha, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.
(7) The alkyne **4** has been prepared from (+)-carene previously: (a) Donkervoort, J. G.; Gordon, A. R.; Johnstone, C.; Kerr, W. J.; Lange, U. *Tetrahedron* **1996**, *52*, 7391. (b) Better yields of **4**, however, were obtained by modifying the reported procedure in two steps. Firstly, the cyclopropanecarboxylic acid **2** was converted to the cyclopropyl methyl ketone according to the protocol of House et al.,[8] and secondly the protocol of Negishi et al.[9] was applied to convert the methyl ketone to the terminal alkyne via the enol phosphate.
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(10) All new compounds were fully characterized by IR, NMR (^{1}H, ^{13}C) mass spectra as well as correct elemental analyses. Spectroscopic data of representative examples are as follows:

Table Cocyclizations of Complex **14** with Various Alkynes and Further Transformations of the Resulting Products **15**/**16** (see Scheme 3).

Entry	R^1	R^2	Products **15** + **16** Yield (%)	Products **17**, **18** Yield (%)	Base[a]	Time [h]	Products **20** Yield (%)[c]	R^{1*}[b]	Triquinane **23** Yield (%)[c]
a	Me	Me	38 + 27	96, 80	NaOH	2.5	–	H	97, 80 (47)
b	Et	Et	37 + 18	97, 46	NaOH	8	–	Me	82, 30 (24)
c	Pr	H	62 (2:1)[d]	90	NaOH	1.5	40[e]	Et	65 (22)
d	iPr	H	44 (1.2:1)[d]	82	NaH	0.5	90 (32)	–	–
e	cPr	H	60 (1.5:1)[d,f]	51 + 34	NaH	0.2	96, 58	–	–
f	Ph	Ph	46[g]	82	NaOH	3	54 (20)	–	–

[a] NaOH was used with an excess of 20 equivalents and NaH of 3 equivalents.
[b] $R^{1*} = R^1$ less one CH_2 group.
[c] Overall yield of dispiroundecenone **20** or triquinane **23** from complex **14** given in parentheses.
[d] Yield of the mixture of **15** + **16** (ratio in parentheses).
[e] Isolated after 0.5 h along with 20% of triquinane **23**.
[f] In this case the two regioisomers with the cyclopropyl group in the 1- and in the 2-position could be separated.
[g] Only **15f** was formed.

Pentacarbonyl[(2*E*/*Z*)-3-dimethylamino-3-{(1′*S*,3′*R*)-*cis*-2′,2′-dimethyl-3′-[2′′-(2′′′-methyl-[1′′′,3′′′]-dioxolan-2′′′-yl)ethyl]cyclopropyl}-1-ethoxy-2-propen-1-yliden]-chromium(5): R_f = 0.56 (*Z*-isomer), R_f = 0.39 (*E*-isomer), Et_2O (10:1)], yellow crystals, mp 75 °C. IR (KBr): 2980 cm^{-1} (C-H), 2912 (C-H), 2769 (C-H), 2044 (C=O), 1969 (C=O), 1889 (C=O), 1527 (C=C), 1431, 1376, 1317, 1254, 1148, 1094, 1069, 1038, 982, 923, 869, 782, 671. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96 (s, 3 H, CH_3), 1.01 (m_c, 1 H, 3′-H), 1.24 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.35 (m_c, 1 H, 1′-H), 1.44 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3), 1.44–1.73 (m, 4 H, 4′′-H, 5′′-H), 3.13 [bs, 6 H, $N(CH_3)_2$], 3.92 (m_c, 4 H, OCH_2CH_2O), 4.65 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 6.25 (s, 1 H, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$, plus DEPT): δ = 15.2 (+, C-3′), 15.5 (+, OCH_2CH_3), 20.8 (–, C-1′′), 23.2 ($C_{quat.}$, C-2′), 23.6 (+, CH_3), 28.5 (+, CH_3), 30.1 (+, C-1′), 32.3 (+, CH_3), 38.8 (–, C-2′′), 41.5 [+, $N(CH_3)_2$], 64.4 (–, OCH_2CH_2O), 72.9 (–, OCH_2CH_3), 109.4 (C_{quat}, C-2′′′), 119.8 (+, C-2), 159.7 (C_{quat}, C-3), 219.3, 224.4 (C_{quat}, C=O), 279.9 (C_{quat}, C-1). – MS (70 eV), *m/z* (%): 501(3) [M^+], 473(13) [M^+ – CO], 445(5) [M^+ – 2CO], 417(6) [M^+ – 3 CO], 389(2) [M^+ – 4 CO], 361(100) [M^+ – 5 CO], 220(21), 204(29), 191(64), 95(25), 87(28), 52(47) [Cr^+], 43(34).

4,5,11,11-Tetramethyltetracyclo[6.4.0.0^{1,5}.0^{10,12}]-dodecan-3,7-dione(10): R_f = 0.25 in Pentane–Et_2O (3:1, colorless crystals, mp 101 °C. IR (KBr): 3010 cm^{-1} (C-H), 2957 (C-H), 2938 (C-H), 2877 (C-H), 1732 (C=O), 1456, 1390, 1376, 1339, 1266, 1206, 1191, 1124, 1100, 1083, 1008, 931, 895, 841, 647, 542, 465. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.02 (d, ^3J = 7.0 Hz, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.23 (dd, ^3J = 6.4, ^3J = 6.4 Hz, 1 H, 10-H), 1.29 (d, ^3J = 6.4 Hz, 1 H, 12-H), 1.88 (ddd, ^2J = 13.8, ^3J = 8.0, ^3J = 6.4 Hz, 1 H, 9-H), 2.01 (AB, d, ^2J = 18.1 Hz, 1 H, 6-H), 2.08 (AB, d, ^2J = 18.1 Hz, 1 H, 6-H), 2.16 (dd, ^2J = 13.8, ^3J = 10.7 Hz, 1 H, 9-H), 2.38 (dq, ^3J = 7.0, ^4J = 1.7 Hz, 1 H, 4-H), 2.40 (AB, d, ^2J = 19.9 Hz, 1 H, 2-H), 2.42 (dd, ^3J = 10.7, ^3J = 8.0 Hz, 1 H, 8-H), 2.78 (dd, ^2J = 19.9, ^4J = 1.7 Hz, 1 H, 2-H). ^{13}C NMR (62.9 MHz, $CDCl_3$, plus DEPT): δ = 9.2 (+, CH_3), 16.3 (+, CH_3), 19.3 (C_{quat}, C-11), 21.5 (+, CH_3), 27.9 (+, CH_3), 29.6 (–, C-9), 30.8 (+, C-10), 37.6 (+, C-12), 48.0 (–, C-2), 49.0 (–, C-6), 50.0 (C_{quat}, C-5), 53.2 (+, C-4), 56.3 (C_{quart}, C-1), 60.9 (+, C-8), 217.9, 218.7 (C_{quat}, C-3, C-7). MS (70 eV), *m/z* (%): 246(24) [M^+], 218(31) [M^+ – CO], 203(11), 190(8), 175(17), 161(8), 148(56), 133(9), 121(100), 105(55).

4,7-Dimethylspiro{cyclopropane-1,11-tricyclo-[6.4.0.0^{1,5}]undeca-4,6-dien-3-one}(23a): R_f = 0.75 in Et_2O, colorless oil. IR(film): 3066 cm^{-1} (C-H), 2948 (C-H), 2915 (C-H), 2854 (C-H), 1695 (C=O), 1641 (C=O), 1587, 1436, 1336, 1246, 1014, 971, 843, 728, 668, 592. ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.65 to –0.25 (m, 1 H, *c*Pr-H), 0.08–0.13 (m, 1 H, *c*Pr-H) 0.16–0.20 (m, 1 H, *c*Pr-H) 0.33–0.38 (m, 1 H, *c*Pr-H), 1.20–1.30 (m, 1 H, 10-H), 1.65 (s, 3 H, CH_3) 1.63–1.73 (m, 1 H, 10-H), 1.92 (s, 3 H, CH_3), 1.96–2.08 (m, 2 H, 9-H), 2.32 (AB, d, ^2J = 16 Hz, 1 H, 2-H), 2.48 (AB, d, ^2J = 16 Hz, 1 H, 2-H), 3.00–3.07 (m, 1 H, 8-H), 6.10 (s, 1 H, 6-H). ^{13}C NMR (62.9 MHz, $CDCl_3$, plus, DEPT): 4.9 (–, *c*Pr-C), 8.7 (+, CH_3), 14.1 (–, *c*Pr-C), 16.5 (+, CH_3), 26.5 (–, C-10), 31.8 (C_{quat}, C-11), 36.9 (& ndash;, C-9), 48.7 (–, C-2), 58.1 (+, C-8), 60.0 (C_{quat}, C-1), 120.9 (+, C-6), 124.8 (C_{quat}, C-5), 162.8 (C_{quat}, C-7), 179.5 (C_{quat}, C-4), 209.6 (C_{quat}, C-3). MS (70 eV), *m/z* (%): 214(100) [M^+], 199(19) [M^+ – CH_3], 185(16) [M^+ – C_2H_5O], 171(35) [M^+ – C_3H_7O], 159(38), 143(21), 132(18), 115(17), 91(16), 77(10), 65(4), 53(4), 41(4).

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(12) Crystallographic data for the angular triquinanes **10** and **23c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-180879(**10**) and CCDC-180718(**23c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).
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